Claims

1. A compound of formula I,

$$R^1O(O)C\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}R^2 \qquad I$$

wherein

R^1 represents $-R^3$ or $-A^1C(O)N(R^4)R^5$ or $-A^1C(O)OR^4$;

A^1 represents C_{1-5} alkylene;

R^2 (which replaces one of the hydrogen atoms in the amidino unit of Pab-H) represents OH, $OC(O)R^6$, $C(O)OR^7$ or $C(O)OCH(R^8)OC(O)R^9$;

R^3 represents H, C_{1-10} alkyl, or C_{1-3} alkylphenyl (which latter group is optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, nitro or halogen);

R^4 and R^5 independently represent H, C_{1-6} alkyl, phenyl, 2-naphthyl or, when R^1 represents $-A^1C(O)N(R^4)R^5$, together with the nitrogen atom to which they are attached represent pyrrolidinyl or piperidinyl;

R^6 represents C_{1-17} alkyl, phenyl or 2-naphthyl (all of which are optionally substituted by C_{1-6} alkyl or halogen);

R^7 represents 2-naphthyl, phenyl, C_{1-3} alkylphenyl (which latter three groups are optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, nitro or halogen), or C_{1-12} alkyl (which latter group is optionally substituted by C_{1-6} alkoxy, C_{1-6} acyloxy or halogen);

R^8 represents H or C_{1-4} alkyl; and

R^9 represents 2-naphthyl, phenyl, C_{1-6} alkoxy or C_{1-8} alkyl (which latter group is optionally substituted by halogen, C_{1-6} alkoxy or C_{1-6} acyloxy);

provided that when R^1 represents R^3, R^3 represents benzyl, methyl, ethyl, *n*-butyl or *n*-hexyl and R^2 represents $C(O)OR^7$, then R^7 does not represent benzyl;

or a pharmaceutically-acceptable salt thereof.

2. A compound of formula I, as defined in Claim 1, wherein A^1 represents C_{1-3} alkylene when R^1 represents $-A^1C(O)N(R^4)R^5$.

3. A compound of formula I, as defined in Claim 1 or Claim 2, wherein R^4 represents H or C_{1-6} alkyl when R^1 represents $-A^1C(O)N(R^4)R^5$.

4. A compound of formula I, as defined in any one of Claims 1 to 3, wherein R^5 represents C_{1-6} alkyl or C_{4-6} cycloalkyl when R^1 represents $-A^1C(O)N(R^4)R^5$.

5. A compound of formula I, as defined in any one of Claims 1 to 3, wherein R^4 and R^5 together represent pyrrolidinyl when R^1 represents $-A^1C(O)N(R^4)R^5$.

6. A compound of formula I, as defined in any one of Claims 2 to 5, wherein A^1 represents C_{1-3} alkylene, and R^4 represents H or C_{1-3} alkyl and R^5 represents C_{2-6} alkyl or C_{5-6} cycloalkyl, or R^4 and R^5 together represent pyrrolidinyl.

7. A compound of formula I, as defined in Claim 1, wherein A^1 represents C_{1-5} alkylene when R^1 represents $-A^1C(O)OR^4$.

8. A compound of formula I, as defined in Claim 1 or Claim 7, wherein R^4 represents C_{1-6} alkyl when R^1 represents $-A^1C(O)OR^4$.

9. A compound of formula I, as defined in Claim 7 or Claim 8, wherein A^1 represents C_{1-5} alkylene and R^4 represents C_{1-4} alkyl.

10. A compound of formula I, as defined in Claim 1, wherein R^3 represents H, C_{1-10} alkyl (which latter group may be linear or, when there are a sufficient number of carbon atoms, may be branched and/or be partially cyclic or cyclic), or C_{1-3} alkylphenyl (which latter groups is optionally substituted, may be linear or, when there are a sufficient

number of carbon atoms, be branched), when R^1 represents R^3.

11. A compound as claimed in Claim 1 or Claim 10, wherein R^1 represents H, linear C_{1-10} alkyl, branched C_{3-10} alkyl, partially cyclic C_{4-10} alkyl, C_{4-10} cycloalkyl, optionally substituted linear C_{1-3} alkylphenyl, optionally substituted branched C_3 alkylphenyl.

12. A compound as claimed in Claim 11, wherein R^1 represents linear C_{1-6} alkyl, C_{6-10} cycloalkyl, or optionally substituted linear C_{1-3} alkylphenyl.

13. A compound of formula I, as defined in any one of Claims 1 to 12, wherein R^2 represents OH.

14. A compound of formula I, as defined in any one of Claims 1 to 12, wherein R^6 represents optionally substituted phenyl or C_{1-17} alkyl (which latter group may be linear or, when there are a sufficient number of carbon atoms, may be branched, be cyclic or partially cyclic, and/or be saturated or unsaturated) when R^2 represents $OC(O)R^6$.

15. A compound as claimed in Claim 14 wherein R^6 represents optionally substituted phenyl, linear C_{1-4} alkyl, branched C_{3-4} alkyl or *cis*-oleyl.

16. A compound as claimed in Claim 15 wherein R^6 represents linear C_{1-3} alkyl or branched C_3 alkyl.

17. A compound of formula I, as defined in any one of Claims 1 to 12, wherein R^7 represents optionally substituted phenyl, C_{1-12} alkyl (which latter group is optionally substituted, may be linear or, when there are a sufficient number of carbon atoms, may be branched, cyclic or partially cyclic, and/or saturated or unsaturated), or C_{1-3} alkylphenyl (which latter

group is optionally substituted, may be linear or, when there are a sufficient number of carbon atoms, may be branched) when R^2 represents $C(O)OR^7$.

18. A compound as claimed in Claim 17 wherein R^7 represents optionally substituted and/or optionally unsaturated linear C_{1-4} alkyl or optionally substituted and/or optionally unsaturated branched C_{3-4} alkyl, optionally substituted phenyl, or optionally substituted linear C_{1-3} alkylphenyl or optionally substituted branched C_3 alkylphenyl.

19. A compound as claimed in Claim 18 wherein R^7 represents optionally substituted linear C_{1-4} alkyl or optionally substituted branched C_{3-4} alkyl, optionally substituted linear C_{1-3} alkylphenyl or branched C_3 alkylphenyl.

20. A compound of formula I, as defined in any one of Claims 1 to 12, wherein R^8 represents H or methyl, when R^2 represents $C(O)OCH(R^8)OC(O)R^9$.

21. A compound of formula I, as defined in any one of Claims 1 to 12 or Claim 20, wherein R^9 represents phenyl, or C_{1-8} alkyl (which latter group is optionally substituted, may be linear or, when there are a sufficient number of carbon atoms, may be branched and/or cyclic or partially cyclic) when R^2 represents $C(O)OCH(R^8)OC(O)R^9$.

22. A compound of formula I, as defined in Claim 20 or Claim 21 wherein R^8 represents H or methyl and R^9 represents phenyl, C_{5-7} cycloalkyl, linear C_{1-6} alkyl, branched C_{3-6} alkyl or partially cyclic C_{7-8} alkyl.

23. A compound as claimed in Claim 22 wherein R^8 represents H and R^9

represents C_{5-7} cycloalkyl, linear C_{1-6} alkyl or partially cyclic C_{7-8} alkyl.

24. A compound as claimed in any one of the preceeding claims wherein, when R^1 represents R^3 and R^3 represents optionally substituted C_{1-3} alkylphenyl, the optional substituent C_{1-6} alkyl.

25. A compound as claimed in Claim 24 wherein the substituent is methyl.

26. A compound as claimed in any one of the preceeding claims wherein, when R^2 represents $C(O)OR^7$ and R^7 represents optionally subsituted C_{1-12} alkyl, the optional substituent is selected from halogen and C_{1-6} alkoxy.

27. A compound as claimed in Claim 26 wherein the substituent is selected from chloro and methoxy.

28. A compound as claimed in any one of the preceeding claims wherein, when R^2 represents $C(O)OR^7$ and R^7 represents optionally subsituted phenyl, the optional substituent is selected from C_{1-6} alkyl, C_{1-6} alkoxy and halogen.

29. A compound as claimed in Claim 28 wherein the substituent is selected from methyl, methoxy and chloro.

30. A compound as claimed in any one of the preceeding claims wherein when R^2 represents $C(O)OR^7$ and R^7 represents optionally subsituted C_{1-3} alkylphenyl, the optional substituent is nitro.

31. A compound as claimed in Claim 1 which is
$EtOOCCH_2$-(*R*)Cgl-Aze-Pab-$COOCH_2CH=CH_2$;
n$PrOOCCH_2$-(*R*)Cgl-Aze-Pab-$COOCH_2CH=CH_2$;

*t*BuOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$CH=CH$_2$;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOEt;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COO-*n*Bu;

PrlC(O)CH$_2$CH$_2$CH$_2$OOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

ChNHC(O)CH$_2$OOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

(*n*Pr)$_2$NC(O)CH$_2$OOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$OOCC(CH$_3$)$_3$;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$OOCC(CH$_3$)$_3$;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH(CH$_3$)OOCCH$_3$;

MeOOCCH$_2$-(*R*)Cgl-Aze-Pab-OOCPh;

MeOOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

BnOOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

*n*PrOOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

*n*PrOOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

*i*PrOOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

*t*BuOOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

(*n*Pr)$_2$NCOCH$_2$OOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

ChNHCOCH$_2$OOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-OAc;

HOOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

HOOCCH$_2$-(*R*)Cgl-Aze-Pab-O-*cis*-Oleyl;

Cyclooctyl-OOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

*t*BuCH$_2$OOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

(2-Me)BnOOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

ChCH$_2$OOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

ChOOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

PhC(Me)$_2$OOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

(Me)$_2$CHC(Me)$_2$OOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

BnOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOPh(4-OMe);

ChCH$_2$OOCCH$_2$-(*R*)Cgl-Aze-Pab-COOPh(4-OMe);

(2-Me)BnOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOPh(4-OMe);

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOPh(4-Me);

BnOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOPh(4-Me);

BnOOCCH$_2$-(*R*)Cgl-Aze-Pab-COO-*n*Bu;

*i*PrOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$CH=CH$_2$;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COO-*i*Bu;

BnOOCCH$_2$-(*R*)Cgl-Aze-Pab-COO-*n*Pr;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$OOCCh;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$OOCCH$_2$Ch;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH(Me)OOCPh;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$OOCPh;

BnOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH(Me)OAc;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$OAc;

*t*BuOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$OAc;

MeOOC-C(=CHEt)CH$_2$-OOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

Men-OOCCH$_2$-(*R*)Cgl-Aze-Pab-COOPh(4-OMe); and

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$CCl$_3$.

32. A compound as claimed in Claim 1 which is

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$CCl$_3$;

BnOOCCH$_2$-(*R*)Cgl-Aze-Pab-COO*n*Bu;

*n*PrOOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

Cyclooctyl-OOCCH$_2$-(*R*)Cgl-Aze-Pab-Z;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-COOCH$_2$OOCCh;

MeOOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

EtOOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

*n*PrOOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

*i*PrOOCCH$_2$-(*R*)Cgl-Aze-Pab-OH;

$BnOOCCH_2$-(*R*)Cgl-Aze-Pab-OH; and
$EtOOCCH_2$-(*R*)Cgl-Aze-Pab-OAc.

33. A compound of formula I, as defined in Claim 1, with the additional proviso that R^1 does not represent $-A^1C(O)OR^4$.

34. A compound of formula I, as defined in Claim 1, with the additional proviso that R^4 and R^5 do not independently represent H.

35. A compound of formula I, as defined in Claim 1, with the additional proviso R^6 does not represent C_{1-17} alkyl, when R^2 represents $OC(O)R^6$.

36. A compound of formula I, as defined in Claim 1, wherein R^1 represents $-A^1C(O)OR^4$.

37. A compound of formula I, as defined in Claim 1, wherein R^4 and R^5 independently represent H.

38. A compound of formula I, as defined in Claim 1, wherein R^6 represents C_{1-17} alkyl, when R^2 represents $OC(O)R^6$.

39. A pharmaceutical formulation including a compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

40. A compound of formula I, as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

41. A compound of formula I as defined in any one of Claims 1 to 38, or

a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where inhibition of thrombin is required.

42. A compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, for use in the treatment of thrombosis.

43. A compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, for use as an anticoagulant.

44. The use of a compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof as active ingredient in the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is required.

45. The use as claimed in Claim 44, wherein the condition is thrombosis.

46. The use of a compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, as active ingredient in the manufacture of an anticoagulant.

47. A method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

48. A method as claimed in Claim 47, wherein the condition is thrombosis.

49. A method as claimed in claim 47, wherein the condition is hypercoagulability in blood and tissues.

50. The use of a compound of formula I, as defined in Claim 1 but without the provisos, as a prodrug.

51. A process for the preparation of compounds of formula I which comprises:

(a) for compounds of formula I in which R^2 represents OH, reaction of a corresponding compound of formula I, wherein R^2 represents $OC(O)R^6$ and R^6 is as defined in Claim 1 with an alkoxide base;

(b) for compounds of formula I in which R^2 represents OH, reaction of a corresponding compound of formula I wherein R^2 represents $C(O)OR^7$ and R^7 is as defined in Claim 1 with hydroxylamine, or an acid addition salt thereof;

(c) reaction of a corresponding compound of formula II,

H-(*R*)Cgl-Aze-Pab-R^2 II

wherein R^2 is as defined in Claim 1 with a compound of formula III,

$R^1O(O)C\text{-}CH_2\text{-}L^1$ III

wherein L^1 represents a leaving group and R^1 is as defined in Claim 1;

(d) for compounds of formula I in which R^1 represents H and R^2 represents OH or $C(O)OR^7$, reaction of a corresponding compound of formula I wherein R^1 represents $C_{1\text{-}10}$ alkyl or $C_{1\text{-}3}$ alkylphenyl, and R^2 represents OH or $C(O)OR^7$, with a base;

(e) for compounds of formula I wherein R^2 represents $OC(O)R^6$ and R^6 is as defined in Claim 1, reaction of a corresponding compound of formula I wherein R^2 represents OH, with a compound of formula IV,

$R^6C(O)\text{-}O\text{-}C(O)R^6$ IV

or a compound of formula V,

$R^6C(O)Hal$ V

wherein Hal$^-$ represents Cl or Br and, in both cases, R^6 is as defined in Claim 1;

(f) for compounds of formula I in which R^1 represents H and R^2 represents $OC(O)R^6$, and R^6 is as defined in Claim 1, reaction of a corresponding compound of formula VI,

$$P^1O(O)C\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}R^2 \qquad VI$$

wherein P^1 represents an acid labile ester protecting group and R^2 represents $OC(O)R^6$, wherein R^6 is as defined in Claim 1, with an acid;

(g) for compounds of formula I in which R^1 represents R^3, R^3 represents $C_{1\text{-}10}$ alkyl or $C_{1\text{-}3}$ alkylphenyl, and R^2 represents OH or $C(O)OR^7$, and R^7 is as defined in Claim 1 by a trans-esterification of a corresponding compound of formula VII,

$$R^{1a}O(O)C\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}R^2 \qquad VII$$

wherein R^{1a} represents a $C_{1\text{-}10}$ alkyl or $C_{1\text{-}3}$ alkylphenyl group other than that being formed, or an alternative labile alkyl substituent and R^2 is as defined in Claim 1.